UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,683	11/15/2001	Avi J. Ashkenazi	P2730P1C32	4971

35489 7590 01/05/2006

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,683	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/27/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Arguments, submitted 27 October 2005, has been entered. Claims 1-118 and 124 were cancelled previously by Applicant (15 November 2001 and 16 June 2004, respectively).

Claims 119-123 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Maintained Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 119-123 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-6 of the previous Office Action (27 July 2005). Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (27 July 2005), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (Remarks/Arguments, 27 October 2005, page 4, for example) that the results presented in the instant Specification are enabling for the antibody that

binds the polypeptide of SEQ ID NO: 351. They argue that the PRO1153 nucleic acid is a diagnostic marker for lung adenocarcinomas and squamous cell carcinomas, and point to the results of the amplification assay. The assay indicated (Table 8, Specification) showed a 2-fold or greater fluorescence in some samples of lung adenocarcinoma (LT7), but not others (LT2 and LT3, among others), as well as positive fluorescence in some samples of lung squamous cell carcinoma (LT4), but not some other samples of lung squamous cell carcinoma (for example, LT9 and LT10).

Applicant's arguments (27 October 2005) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing an increase in DNA copy number- about 2 fold or greater- in some lung tumors, but not others. However, there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are also increased in these cancers. Furthermore, as discussed in the previous Office Action (27 July 2005, pages 4 and 5), what is often seen is a lack of correlation between DNA amplification and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to the results presented, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered

that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

The specification of the instant application does not complement the low (2-fold) PRO1153 gene expression data with any mRNA or protein studies. The skilled artisan would not reasonably assume that PRO1153 polypeptide is overexpressed in certain lung or cancer tumors, based on the disclosure, without actually testing for PRO1153 polypeptide overexpression. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. Firstly, the instant disclosure does not show reliable fluorescence of PRO1153 even within the same experimental group. Secondly, it is presumed that gene amplification predicts increased mRNA production. Thirdly, it is presumed that increased mRNA production leads to increased protein production. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. The instant specification does not disclose that PRO1153 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples.

Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1153 protein could be used as a cancer diagnostic. In addition, the instant Specification does not provide proper statistical analysis such as reproducibility, standard error rates, etc. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

Applicants assert that the Patent Office has failed to meet its initial burden of proof that claims of Utility are not substantial or credible. They contend that the examiner's reasoning is based on a misrepresentation of the scientific data presented in the cited references and application of an improper, heightened legal standard. Applicants state that whether the PRO gene is amplified in few tumor samples or in the vast number of tumor samples is not relevant to its utility as a tumor marker (27 October 2005, page 5).

Applicant's arguments have been fully considered but are not found to be persuasive. The truth or credibility of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Pennica et al. (cited in the previous Office Action) and Hu et al. (who reviewed 2286 genes reported in the literature to be associated with breast cancer). These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1153 polypeptide is not useful as a cancer diagnostic agent.

Applicants indicate that the PRO1153 nucleic acid was amplified in a significant number of lung tumors and showed a large increase in gene copy number, i.e., at least 2-fold amplification. At page 6 of the Response, Applicants argue that the amplification of the nucleic acid encoding the disclosed polypeptide is significant for the detection of lung cancer and cite the Declarations under 37 CFR § 1.132. However, no substantially new arguments have been presented. Except for the Goddard declaration, these declarations were previously considered and discussed by the Examiner in the Office Action of 17 March 2004. However, it is again noted that the PRO1153 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1153 nucleic acid was amplified in about 25% of the cancer samples studied. No mutation or translocation of PRO1153 has been associated with any type of cancer. In addition, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung. For these reasons, it is not clear that the reported amplification is meaningful. In the absence of any of the above information, all that the specification has done is present evidence that the DNA encoding PRO1153 is amplified in some cancer samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Therefore, based on the totality of the evidence, it is maintained that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO1153 are specifically amplified in lung tumors. Further research would have to be done in order to determine if PRO1153 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to reasonably confirm the usefulness of PRO1153 protein as a lung cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

The fact remains that the instant specification does not disclose whether or not PRO1153 gene or protein is reliably overexpressed in any tumor tissues. Only about 25% of the experimental samples tested positive, even within each tumor type, and subtype. For these reasons the skilled artisan must perform further research in order to reasonably confirm overexpression and specificity of positive fluorescence. The requirement for such further research indicates that the asserted utility of PRO1153 as a cancer diagnostic agent is not substantial. The specification does not disclose the expression levels of PRO1153 protein in any tumor samples; such would have to be determined through further research on the part of the skilled artisan. Thus, even the utility proposed regarding the usefulness of PRO1153 protein in the diagnosis of cancer is not substantial. Finally, there is no disclosure regarding what treatment modality should be chosen by the clinician based on whether or not PRO1153 polypeptide is overexpressed. The determination of such constitutes further experimentation, indicating

that the asserted utility is not substantial. Since the disclosed protein lacks utility, there would be no reason to use the claimed antibody to detect the protein.

Applicants conclude that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed. They argue that the PRO1153 polypeptides and claimed antibodies have utility in the diagnosis of cancer, and, based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner concedes that the specification teaches how to make PRO1153 polypeptide. However, the specification fails to provide a substantial asserted utility for the claimed PRO1153 polynucleotides, and thus the specification also fails to enable the claimed PRO1153 polypeptides and antibodies (specifically, the specification fails to teach the skilled artisan how to use the claimed PRO1153 polypeptides without undue experimentation). As discussed above, PRO1153 genomic DNA was found to be slightly amplified in only about 25% of types and subtypes of lung cancer samples compared to a normal DNA control. The data were not corrected for aneuploidy, which was known to be common in cancerous *and non-cancerous* lung tissue. Thus, it is not clear from the gene amplification data whether or not PRO1153 genomic DNA actually is amplified in certain lung tumors. Second, the literature reports that gene amplification often does not correlate with increased mRNA levels (see Pennica et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy

tissue (see Haynes et al.) or cancerous tissue (see Hu et al). In view of the totality of the evidence, the skilled artisan would not reasonably assume that PRO1153 polypeptide is overexpressed in certain lung tumors based on the disclosure regarding gene amplification without actually testing for PRO1153 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. Fourth, based on the gene amplification data, the skilled artisan *also* would not presume that PRO1153 polypeptide is *not* overexpressed in certain lung tumors without actually testing for PRO1153 polypeptide levels. In view of such and the lack of guidance regarding how the physician would use information regarding PRO1153 polypeptide overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO1153 polypeptide as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement is proper.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
29 December 2005

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER